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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/892,981	06/27/2001	Roland Gerritsen van der Hoop	01722906	3783

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EXAMINER	
HUI, SAN MING R	
ART UNIT	PAPER NUMBER
1617	9

DATE MAILED: 08/27/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/892,981	VAN DER HOOP, ROLAND GERRITSEN	
	Examiner	Art Unit	
	San-ming Hui	1617	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29 and 45-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-29 and 45-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendments of claims 1 and 45 filed June 7, 2002 have been entered.

Claims 1-29 and 45-73 are pending.

The claims are now directed to a method of treating, preventing or reducing the risk of developing a menopause disorder by administering a sex-hormone binding synthesis inhibiting agent in an oral dosage unit and at least one steroid in a non-oral dosage unit.

The outstanding rejections of claims 1 and 45 under 35 USC 112, second paragraph in regard to "non-orally deliverable pharmaceutically acceptable steroids" have been withdrawn in view of the amendment filed June 7, 2002.

Please note that the expression, "a method of ... preventing ... the risk of developing a menopause disorder" in claims 1 and 45 renders the claims indefinite as failing to clearly set forth the metes and bounds of the patent protection desired. Examples of how and when to prevent the risk of developing a menopause disorder are not set forth in the specification. Absent such exemplification, the skilled artisan could not establish the identity of those situations wherein prevention of the risk of developing a menopause disorder would be effected. Furthermore, it is unclear as to the degree of prevention (e.g., total prevention, some prevention, probable prevention, total prevention in most cases...etc.) herein because the specification does not disclose the extent of prevention achieved. Examiner would favorably consider the term "prophylaxis" over "prevention".

Examiner also notes that claims 13, 19, 57, and 63 contain the trademark/trade name "CARBOPOL". Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe a pharmaceutical excipients containing polyethylene glycol (PEG) and, accordingly, the identification/description is indefinite.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-29, 45-73 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The expression "menopause disorders" in claims 1 and 45 renders the claims indefinite as to the disorders or conditions encompassed thereby. The instant specification, page 21, line 8-16 attempts to define the expression "menopause

disorders"; however, it is not clear that peri-menopausal conditions, which are encompassed by the expression "menopause disorders", are encompassed by the claims.

Response to the arguments regarding rejections under 35 USC 112, second paragraph

It is not clear what disorders, other than those listed as examples in the instant specification, page 21, line 8-16, would be encompassed by the claims as "menopause disorders". In addition, please note that even the examples listed are vague and the scope of the invention is not defined. For examples, cardiovascular disorder – does the term menopause disorder include arrhythmia such as ventricular fibrillation? If it does encompass this disorder, then the specification may not enable the treatment or prevention of specific cardiovascular disorder.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-29 and 45-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rubin (US Patent 5,5059,603), Ebert et al. (US Patent 5,152,997), and Place (US Patent 6,117,446) in view of Langtry et al. (Drugs 1999; 57(6): 967-989), Remington's Pharmaceutical Sciences (1990, 18th ed., pages 1305 and 1314), Merck Index (11th ed., 1989, page 821, monograph 5103), Hofman et al. (US Patent

4,563,473), and Atkinson et al. (US Patent 4,442,094), references of record in previous office action mailed December 17, 2002.

Rubin teaches methyl testosterone is useful in a method of treating androgen deficiency associated disorders such as impotence (See particularly col. 2, line 59 - col. 3, line 11).

Ebert et al. teaches testosterone therapy is a useful in a method of treating male hypogonadism and the conditions associated male hypogonadism comprising employing a matrix containing testosterone and penetration enhancer onto the skin (See col. 1, line 20-66).

Place teaches a method of hormonal replacement therapy and symptoms thereof such as female sexual dysfunction and vaginal dryness comprising a treatment of a woman with an estrogen such as estradiol and an androgenic steroid such as testosterone and methyltestosterone (See col. 7, line 35; col. 11, line 6-61). Place also teaches that the dosage of the estradiol may be 0.05 to 0.5 mg (See col. 11, line 36-61). Place also teaches that the dosage of the androgenic agent such as testosterone to be 0.1 to 2.5mg (See col. 11, line 44-45). Place also teaches that the estradiol and/or testosterone can be formulated in oral dosage form such as lozenges and tablets (See col. 12, line 29).

The references do not expressly teach the dosage form of the instant invention to be a gel comprising isopropyl myristate, ethanol, and Carbopol. The references do not expressly teach the employment of the composition containing the combination of testosterone and methyltestosterone or the combination of estradiol and

methyltestosterone. The references do not expressly the dosage of methyltestosterone to be 0.2 mg to about 50.0mg and that of testosterone or estradiol to be 0.1g to about 100.0g. The references do not teach the employment of sildenafil in the method herein.

Langtry et al. teaches that sildenafil is useful to treat erectile dysfunction (See abstract).

Remington's Pharmaceutical Sciences teaches that ethanol is a commonly used pharmaceutical solvent (See page 1314-1315). Remington's Pharmaceutical Sciences also teaches that carbopol is a commonly used pharmaceutical excipient as thickening agent (See page 1305).

Merck Index teaches that Isopropyl myristate is useful in topical pharmaceutical preparation where good penetration through skin is desired (See page 821, col. 1).

Hofman et al. teaches that ethanol, Carbopol, and Isopropyl myristate are typical agents for formulating gel (See col. 2, line 19-35).

It would have been obvious to one skill in the art when the invention was made to employ a gel formulation comprising sildenafil and the actives, estradiol and methyltestosterone or testosterone and methyltestosterone, in the dosage herein and ethanol, Carbopol, and Isopropyl myristate as the excipients in a method of treating menopausal disorders in a mammal.

One of ordinary skill in the art would have motivated to employ a gel formulation comprising sildenafil and the actives: estradiol and methyltestosterone, or testosterone and methyltestosterone, in the dosage herein and ethanol, Carbopol, and Isopropyl myristate as the excipients in a method of treating menopausal disorders in a mammal

because estradiol, testosterone, and methyltestosterone are all known in the art to be useful in method of treating both male and female menopausal disorders. Employing two of these agents which are known to be useful to treat menopausal disorders individually into a single method useful for the very same purpose is *prima facie* obvious, absent evidence to the contrary. See *In re Kerkhoven* 205 USPQ 1069. Further employing sildenafil with testosterone and/or methyltestosterone, which are known to be useful in treating impotence individually, in a method useful for the very same purpose would be *prima facie* obvious. Furthermore, the optimization of result effect parameters (e.g., dosage range of the active) is obvious as being within the skill of the artisan. Moreover, interchanging the dosage form of the menopausal disorder treating composition into a gel preparation and employing common excipients in the same is within the purview of skilled artisan. The selection of one or another well-known excipients would be seen as a simple selection from among obvious alternatives, absent evidence to the contrary.

It is applicant's burden to demonstrate unexpected results over the prior art. See MPEP 716.02, also 716.02 (a) - (g). Furthermore, the unexpected results should be demonstrated with evidence that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance. *Ex parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992). Moreover, evidence as to any unexpected benefits must be "clear and convincing" *In re Lohr*, 137 USPQ 548 (CCPA 1963), and be of a scope reasonably commensurate with the scope of the subject matter claimed, *In re Linder*, 173 USPQ 356 (CCPA 1972). In the instant case, examples 1-6 in the

instant specification page 38-42, have been considered, but are not found persuasive. The examples are merely showing the effectiveness of treating menopause disorders by employing the combination of the herein claimed hormonal agents. This is seen to be an expected effect based on the cited prior art. No convincing and clear unexpected result is seen.

Response to Arguments

Applicant's rebuttal arguments averring Rubin's teaching away filed June 8, 2002 have been fully considered but they are not persuasive. Rubin is merely teaching the side effects of methyltestosterone. Please note that every drug would have certain side effects. When taking the cited prior art together, as a whole, administering different hormonal agents together would be reasonably expected to reduce the dose of methyltestosterone, and therefore, would minimize the adverse effect of methyltestosterone thereby.

Applicant's rebuttal arguments averring Place et al. failing to teach oral dosage unit filed June 8, 2002 have been fully considered, but they are not persuasive. Place et al. clearly teaches the estradiol and testosterone and/or methyltestosterone can be formulated into dosage forms such as lozenges and tablets (See col. 12, line 29), which are the preferred dosage forms recited in the instant claims 3 and 47.

Applicant's arguments filed June 8, 2002 have been fully considered but they are not persuasive. Applicant argues that contrary to Examiner's citation of *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980), it is not necessarily *prima facie* obvious to combine two or more components, each of which is taught by the prior art to be useful for the same

purpose. In support of his assertion applicant cites to *In re Geiger*, 2 USPQ2d 1276 (Fed. Cir. 1987). Note that the court's analysis in *Geiger* was based on the notion of "non-analogous" art and the combining of elements from different (i.e., non-analogous) arts. The case at bar is therefore distinguishable from *Geiger*. Here, all the elements are known to be useful in treating both male and female menopausal disorders in the pharmaceutical arts. The idea of combining them flows logically from their having been individually taught in the prior art, *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980). As the same token, sildenafil and testosterone and/or methyltestosterone, which are also known to be useful in treating impotence individually. Combining these various components into a single composition would have therefore been obvious, absent evidence to the contrary. No such evidence is seen.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (703) 305-1002. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Russell Travers, J.D., can be reached on (703) 308-4603. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

RUSSELL TRAVERS
PRIMARY EXAMINER
GROUP 1200

San-ming Hui
August 26, 2002